Evaluating safety of thrombolysis in chronic kidney disease patients presenting with pulmonary embolism using propensity score matching.

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Evaluating safety of thrombolysis in chronic kidney disease patients presenting with pulmonary embolism using propensity score matching

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Abstract To assess the safety of thrombolytic therapy in chronic kidney disease (CKD) patients who present with pulmonary embolism (PE). We used the Nationwide Inpatient Sample Database to identify patients who underwent thrombolysis for PE between 2010 and 2014. The patients were divided into two groups: (1) No CKD and (2) CKD. Patients with and without CKD were matched using 1:1 propensity score matching and a caliper width of 0.01. The primary outcomes were in-hospital mortality and hemorrhagic events. The secondary outcomes were blood transfusions, length of stay and total hospitalization charge. Two separate, multivariate analyses were also performed to determine the predictors for primary outcomes. The No CKD group had 16,238 and CKD group had 1341 patients prior to matching. Patients with CKD were older (Median age 67 vs. 57 years; $p<0.01$), male (60.6 vs. 51.8%) and had a higher prevalence of coronary artery disease, congestive heart failure, diabetes, hyperlipidemia, hypertension, and prior stroke among other comorbidities. They also had significantly higher rate of in-hospital mortality (OR 1.66) and hemorrhagic events (OR 1.47) prior to matching. Post-matching, there was no difference in hospital mortality (22.9 vs. 21.8%; $p=0.51$) or hemorrhagic events (3.8 vs. 3.0%; $p=0.27$) between CKD and No CKD groups. Patients with CKD had a longer length of stay, but no difference in proportion of patients receiving a blood transfusion and total hospitalization charges post-matching. Multivariate analysis showed that CKD did not predict mortality (OR 0.88, 0.75–1.02; $p=0.09$) or hemorrhagic events (OR 0.89, 95% CI 0.76–1.04; 0.13). There was no increase in rate of hospital mortality or hemorrhagic events among CKD patients who underwent thrombolysis for PE.

Keywords Pulmonary embolism · Thrombolysis · Bleeding · Nationwide Inpatient Sample Database

Introduction

The use of thrombolytics in hemodynamically unstable patients presenting with pulmonary embolism (PE) is recommended for its ability to restore rapid circulation compared to anticoagulants [1–3]. A pooled analysis of 16 trials (included low, intermediate and high-risk PE) has shown that thrombolysis for PE patients is associated with lower mortality and increased risk of bleeding [4]. However, the use of thrombolytic agents for sub-massive PE is controversial. The increased bleeding risk with thrombolytic therapy has been well documented.

Presence of underlying chronic kidney disease (CKD) is considered an important risk factor when weighing the risk of bleeding against the benefit of thrombolytic therapy. While CKD itself may create a hypercoagulable milieu,

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uremic platelet dysfunction increases the risk of bleeding, especially as CKD progresses to end-stage renal disease (ESRD) [5, 6]. Studies on the use of tissue plasminogen activator (tPA) among CKD patients with an ischemic stroke have been controversial with evidence for both increased bleeding and no difference in bleeding in comparison to those with normal kidney function [7, 8]. Data on use of thrombolytics among CKD patients presenting with acute PE is scarce. We designed our study to explore whether patients with CKD who receive thrombolytic therapy for the treatment of acute PE are at an increased risk of bleeding complications and in-hospital death.

Methods

We analyzed data using the Nationwide Inpatient Sample (NIS), a subset of Agency for Healthcare Research and Quality from 2010 to 2014 [9]. The database reflects 20% of admissions across nearly 1000 hospitals across the United States and it is the largest all-payer in-patient database; we used weighted cases. International Classification of Disease-Ninth Revision-Clinical Modification (ICD-9) codes were used to identify the cases. The database provides ICD-9 procedure codes and Clinical Classification Software (CCS), which are clusters of similar diagnoses grouped into a single code, as well as Elixhauser comorbidities. We have listed all the ICD 9 and CCS codes and Elixhauser comorbidities that were used for the study.

We identified patients with PE (ICD 9 codes: 415.0, 415.1, 415.13 and 415.19), and intravenous thrombolytic administration (using ICD 9 procedure code: 99.10). Catheter-directed thrombolysis was assumed if patients had pulmonary angiography (ICD-9 procedure code: 88.43) [10]. Patients were included in the study if they had PE as a primary diagnosis and procedure code for thrombolytic therapy listed at any position in the procedure columns within the database. We excluded patients if they were transferred out of the hospital, or had: acute ischemic stroke, ST elevation myocardial infarction, chronic blood loss anemia, gastritis, peptic ulcer, diverticular disease, or malignancy and solid tumors. Cases with missing values for age, race and gender were also excluded since these variables were used to perform propensity score matching (PSM) analysis. Selected cases were grouped into two categories: Patients without CKD (No CKD group) or with CKD (CKD group). The CKD patients were identified with ICD-9 codes 585.1, 585.2, 585.3, 585.4, 585.5, 585.6 and 585.9. Outcomes of interest were intracranial hemorrhage (ICD-9 codes: 430, 431, 432, 432.0, 432.1 and 432.9), gastrointestinal hemorrhage (CCS code: 153), and in-patient mortality. We also reported summation of both incidences of intracranial hemorrhage and gastrointestinal bleed as hemorrhagic events. The information of in-patient mortality was provided in the database. Since the database has de-identified patient information and it is a publicly available database, the study was exempted from the Institutional review board committee [11].

Statistical analysis

Statistical analysis was performed on IBM SPSS, version 23 (IBM Corporation, Armonk, NY, USA). PSM analysis was done on unweighted cases to match the CKD patients to those with no CKD using a 1:1 ratio. Using caliper width of 0.01, logistic regression algorithm and nearest neighbor variable method, we retained 88% of weighted cases (1180 out of 1341) from the CKD group. Age, gender, Caucasian race, alcohol abuse, smoking status, iron deficiency anemia, congestive heart failure, chronic lung conditions, coagulopathy, hypertension, liver disease, obesity, peripheral vascular disease, history of cerebrovascular accident, long-term warfarin and aspirin use, acute kidney injury, coronary artery disease, hemodialysis, catherter-directed thrombolysis, dyslipidemia, and diabetes were included for PSM. Categorical variables were analyzed with Chi square test, and reported as number of cases and percentages. Prior to analyzing continuous variables (age, length of stay and total charges), we determined that the variables were non-parametric based on Kolmogorov–Smirnov test. Therefore, we used Mann–Whitney U test to analyze these variables. We reported their median and interquartile ranges. Our analysis and reporting of the data included both before and after PSM. The length of stay was calculated after excluding patients who died during the hospitalization. To assess whether CKD is an independent predictor of hemorrhagic events or in-hospital mortality, we used multivariate logistic regression by adjusting for the same variables that were entered into the PSM algorithm. Odds ratios (OR) were reported with 95% confidence interval (CI). A p value <0.05 was taken as statistically significant.

In addition to PSM, we created two separate multivariate logistic regression models to identify independent predictors for primary outcomes, hemorrhagic events and in-hospital mortality. For the hemorrhagic events model, the following variables were included: age, gender, Caucasian race, alcohol abuse, smoking status, iron deficiency anemia, congestive heart failure, CKD, chronic lung conditions, coagulopathy, hypertension, liver disease, obesity, peripheral vascular disease, history of cerebrovascular accident, long-term warfarin and aspirin use, acute kidney injury, coronary artery disease, hemodialysis, catheter-directed thrombolysis, dyslipidemia, and diabetes. The same variables, as well as hemorrhagic events, were included within the in-hospital mortality model.

Results

Patient characteristics

Prior to matching, patients in the CKD group were older (median age: 67 vs. 57 years; $p < 0.001$), had more males (60.6 vs. 51.8%; $p < 0.001$) and less Caucasians (64.3 vs. 68.0%; $p = 0.006$). In addition, the CKD group had patients with more comorbidities. Briefly, the CKD group had proportionally higher numbers of patients with coronary artery disease, congestive heart failure, chronic lung disease, coagulopathy, anemia, diabetes, dyslipidemia, prior cerebrovascular accidents, liver disease, obesity, peripheral vascular disease, acute renal injury and use of hemodialysis (Table 1).

All variables except for chronic anticoagulant use selected for PSM were matched between the two groups. The final cohort included 2353 weighted cases: 1173 (49.9%) in No CKD and 1180 (50.1%) in the CKD groups. There was no statistical difference between No CKD or CKD groups for age (65 vs. 65 years, $p = 0.80$); male gender (39.9 vs. 42.0%; $p = 0.30$); and other comorbidities except for chronic anticoagulant use, which was more prevalent in the CKD group (8.0 vs. 4.5%, $p = 0.001$). There was no statistical difference between the groups for other variables except there were more Caucasians in the No CKD group (70.7 vs. 64.8%) (Table 1).

Primary and secondary outcomes

Before matching, significantly higher proportion of hemorrhagic events and in-hospital mortality occurred in CKD group with OR 1.62 (95% CI 1.41–1.85; $p < 0.001$) and OR 1.67 (95% CI 1.26–2.19; $p < 0.001$), respectively. After matching, the risk of in-patient mortality OR 1.07 (95% CI 0.88–1.30; $p = 0.51$) and hemorrhagic events OR 1.29 (95% CI 0.82–2.02; $p = 0.27$) were not statistically significant. Prior to matching the need for transfusion was higher in the CKD group OR 1.79 (95% CI 1.50–2.15; $p < 0.001$), but it did not reach significance after the match OR 1.33 (95% CI 0.99–1.73; $p = 0.06$). The median cost of hospital charges and length of stay was higher in the CKD group before but not after propensity matching. The median hospital cost (in US dollars) was $73,720 (95% CI $45,283–108,457) and $73,570 (95% CI $47,285–118,768) for No CKD and CKD,

Table 1 Baseline characteristics of patients before and after propensity score matching analysis

Variables	Before matching		p value	After matching		p value
	No CKD n = 16,238	CKD n = 1341		No CKD n = 1173	CKD n = 1180	
Median age in years (IQR)	57 (45–67)	67 (56–76)	<0.001	65 (56–72)	65 (54–73)	0.80
Males, n (%)	8416 (51.8)	812 (60.6)	<0.001	469 (39.9)	496 (42.0)	0.30
Caucasians, n (%)	5202 (68.0)	862 (64.3)	0.006	829 (70.7)	764 (64.8)	0.002
Alcohol abuse[a], n (%)	612 (3.8)	40 (3.0)	0.14	25 (2.1)	35 (3.0)	0.20
CAD, n (%)	2162 (13.3)	374 (27.9)	<0.001	299 (25.5)	290 (24.6)	0.62
CHF[a], n (%)	2236 (13.8)	328 (24.5)	<0.001	237 (20.2)	253 (21.5)	0.45
Chronic lung disease[a], n (%)	2900 (17.9)	264 (19.7)	0.09	243 (20.7)	240 (20.4)	0.83
Coagulopathy[a], n (%)	1787 (11.0)	242 (18.0)	<0.001	210 (17.9)	198 (16.8)	0.48
Deficiency anemia[a], n (%)	2561 (15.8)	332 (24.8)	<0.001	259 (22.1)	257 (21.8)	0.87
Diabetes Mellitus[a], n (%)	3574 (22.0)	557 (41.5)	<0.001	415 (35.4)	459 (38.9)	0.08
Dyslipidemia, n (%)	5084 (31.3)	614 (45.8)	<0.001	518 (44.2)	519 (44.0)	0.95
History of CVA, n (%)	535 (3.3)	80 (6.0)	<0.001	66 (5.6)	70 (5.9)	0.75
Hypertension[a], n (%)	8872 (54.6)	1129 (84.1)	<0.001	990 (84.4)	967 (81.9)	0.11
Liver disease[a], n (%)	313 (1.9)	35 (2.6)	0.09	45 (3.8)	35 (3.0)	0.25
Long term coumadin use, n (%)	1274 (7.8)	94 (7.0)	0.27	53 (4.5)	94 (8.0)	0.001
Long term Aspirin use, n (%)	1105 (6.8)	138 (10.3)	<0.001	129 (11.0)	123 (10.4)	0.66
Obesity[a], n (%)	5413 (33.3)	491 (36.6)	0.02	425 (36.2)	456 (38.6)	0.22
Catheter-directed thrombolysis	4326 (26.6)	335 (25.0)	0.18	316 (26.9)	285 (24.2)	0.12
Smoking, n (%)	4323 (26.6)	350 (26.1)	0.68	304 (25.9)	325 (27.6)	0.37
PVD[a], n (%)	643 (4.0)	126 (9.4)	<0.001	100 (8.5)	82 (7.0)	0.15
AKI, n (%)	2737 (16.9)	698 (52.1)	<0.001	525 (44.8)	551 (47.0)	0.34
Hemodialysis, n (%)	2054 (12.6)	330 (24.6)	<0.001	275 (23.4)	265 (22.5)	0.58

CKD chronic kidney disease, *IQR* interquartile range, *CAD* coronary artery disease, *CHF* congestive heart failure, *CVA* cerebrovascular accident, *PVD* peripheral vascular disease, *AKI* acute kidney injury

[a]Denotes Elixhauser comorbidity

Table 2 Primary and second outcomes before and after propensity score matching

	Before matching		p value	After matching		p value
	No CKD	CKD		No CKD	CKD	
	n = 16,238	n = 1341		n = 1173	n = 1180	
Primary outcomes						
Hemorrhagic events, n (%)	444 (2.7)	60 (4.5)	<0.001	35 (3.0)	45 (1.9)	0.27
GI bleed, n(%)	334 (2.1)	45 (3.4)	0.002	25 (2.1)	30 (2.5)	0.51
ICH, n (%)	125 (0.8)	15 (1.1)	<0.001	16 (1.4)	15 (1.3)	0.85
In-patient mortality, n (%)	2448 (15.1)	299 (22.3)	<0.001	256 (21.8)	271 (23.0)	0.51
Secondary outcomes						
Blood transfusion, n(%)	1081 (6.7)	152 (11.3)	<0.001	99 (8.4)	127 (10.8)	0.06
Length of stay in days (IQR)	6 (4–8)	7 (5–10)	<0.001	6 (5–9)	7 (5–10)	<0.001
Total charges in US dollars (IQR)	66,909 (45,646–99,635)	73,570 (47,285–114,205)	<0.001	73,720 (45,283–108,457)	73,570 (47,285–118,768)	0.11

GI gastrointestial, *ICH* intracranial hemorrhage, *IQR* interquartile range

respectively, but was not significant after propensity matching (Table 2). The multivariate logistic regression models did not predict CKD as an independent predictor of in-hospital mortality, OR 0.89 (95% CI 0.76–1.04; p = 0.13), or hemorrhagic events OR 1.20 (95% CI 0.89–1.62; p = 0.23) (Tables 3, 4).

The multivariate analysis shows that presence of CKD does not independently predict incidence of either hemorrhagic events (OR 0.89 95% CI 0.76–1.04; p = 0.13) or in-hospital mortality (OR 0.88, 95% CI 0.75–1.02; p = 0.09). The strongest predictor for both primary outcomes was acute kidney injury, while catheter directed thrombolysis was associated with reduction in the primary outcome. Increasing age was associated with incremental risk of the primary outcomes (Table 4).

Discussion

The findings from our analysis show that after PSM, there is no difference in hemorrhagic events or in-patient mortality in those with and without CKD who receive thrombolytic therapy for the diagnosis of (PE). In addition, there were no significant differences between secondary outcomes, blood transfusion, length of stay and median hospital charges.

To the best of our knowledge this is the first study to assess the outcomes among CKD patients presenting with an acute PE who receive thrombolytic therapy. Kumar et al. found that the incidence of PE was 527 per 100,000 in patients with ESRD, 204 per 100,000 in patients with CKD and 66 per 100,000 in patients without CKD [5]. Patients with CKD experience higher rates of atherothrombotic manifestations and have a higher thromboembolic potential [6]. Studies have reported that patients with CKD also have an increased risk of bleeding complications [12–14]. In fact, platelet dysfunction has been attributed as a primary cause for bleeding in the presence of CKD. This cascade involves defective platelet adhesion to sub-endothelium, defective platelet aggregation partially due to decreased GPIIb/IIIa receptor expression and uremic toxins that inhibit fibrinogen binding to GPIIb/IIIa [6, 12–14]. Conversely, uremic platelets also display features of pro-coagulant activity such as increased thrombin generation, phosphatidylserine exposure and higher concentration of von Willebrand factor and

Table 3 Odd-ratios of primary and secondary outcomes

Before matching			After matching	
Variable	Odd ratio (95% CI)	p value	Odd ratio (95% CI)	p value
Primary outcomes				
Hemorrhagic events, n(%)	1.67 (1.26–2.19)	<0.001	1.29 (0.82–2.02)	0.27
GI bleed, n (%)	1.65 (1.20–1.27)	0.002	1.20 (0.70–2.05)	0.51
ICH, n (%)	1.46 (0.85–2.50)	<0.001	0.93 (0.46–1.90)	0.85
In-patient mortality, n(%)	1.62 (1.41–1.85)	<0.001	1.07 (0.88–1.30)	0.51
Secondary outcome				
Blood transfusion	1.79 (1.50–2.15)	<0.001	1.31 (0.99–1.73)	0.06

GI gastrointestinal, *ICH* intracranial hemorrhage

Table 4 Multivariate analysis for primary outcomes

Variable	Odd ratio (95% confidence interval)	p value
Independent predictors for hemorrhagic events[a]		
Prior cerebrovascular accident	1.87 (1.52–2.30)	<0.001
Acute kidney injury	3.50 (3.18–3.87)	<0.001
Catheter-directed thrombolysis	0.42 (0.38–0.48)	<0.001
Age	1.03 (1.02–1.03)	<0.001
Chronic kidney disease	0.89 (0.76–1.04)	0.13
Liver disease	1.50 (1.14–1.98)	0.004
Independent predictors for mortality[b]		
Acute kidney injury	3.38 (3.06–3.74)	<0.001
Catheter-directed thrombolysis	0.43 (0.38–0.48)	<0.001
Age	1.03 (1.02–1.04)	<0.001
Chronic kidney disease	0.88 (0.75–1.02)	0.09
Hemorrhagic event	3.86 (3.15–4.72)	<0.001

[a]The model was adjusted for age, gender, Caucasian race, alcohol abuse, smoking status, iron deficiency anemia, congestive heart failure, chronic kidney disease, chronic lung conditions, coagulopathy, hypertension, liver disease, obesity, peripheral vascular disease, history of cerebrovascular accident, long-term warfarin and aspirin use, acute kidney injury, coronary artery disease, hemodialysis, Catheter-directed thrombolysis, dyslipidemia, and diabetes

[b]The model included all variables used in the first model and hemorrhagic events

platelet derived micro-particles [6, 12–15]. Combined with an understanding of the pathophysiologic mechanisms of CKD and such data, physicians can be reluctant to administer thrombolytic therapy to patients with PE.

Prior to PSM, the CKD group had disproportionately more comorbidities including AKI, which was an independent predictor of the primary outcomes. Once propensity matching was performed, outcomes such as in-hospital mortality and incidence of hemorrhagic events were not different. Indeed, the multivariate analysis showed that age and comorbidities such as AKI and liver disease were associated with higher risk of mortality among the study population, but CKD did not increase the risk of either of the primary outcomes. These findings suggest that the primary outcomes were related to other morbidities. In contrary, catheter directed thrombolysis was associated with a reduced risk of the primary outcomes. Due to its ability to reduce bleeding risk and improve short and long term outcomes, catheter directed thrombolysis is an attractive option [16]. In a study of stroke patients with CKD who received tPA, there were higher unadjusted odds of symptomatic intracranial hemorrhage or serious systemic hemorrhage, but this was explained by non CKD related factors [17]. The authors reported that the incidence of systemic hemorrhage was 0.99%, and symptomatic intracranial hemorrhage was 4.62%; in-hospital mortality was 7.94%. In our study, the incidence of intracranial hemorrhage was 1.3% (after matching) because we excluded patients with ischemic stroke, as ischemic stroke is known to be associated with hemorrhagic conversion [18]; thus we eliminated the possibility of hemorrhagic conversion related intra-cranial hemorrhage. The incidence of intracranial hemorrhage could be attributed to direct administration of thrombolytic agent in our study. Massive PE with hemodynamic collapse is associated with a very high mortality range. Estimates range from 8 to 64% and vary depending on several patient related factors present on admission: such as cardiogenic shock, hemodynamic instability, cardiac arrest, RV dysfunction and presence of other co-morbidities [19]. The varying rates of mortality in association with varying acuity of patient presentation makes it difficult to compare our mortality rate with that of other studies. While our study did find an unmatched mortality rate of 15.1% in the no CKD group and 22.3% in the CKD group, this includes all patients who received thrombolytic therapy. Given current guidelines for the use of thrombolytic therapy we suspect that the higher mortality rate in our study was due to the higher acuity of patients on presentation, such that tPA was even a consideration for use.

Currently, there remains no consensus on the use of thrombolytic agents for the treatment of sub-massive PE, defined as hemodynamically stable PE with signs of right ventricular dysfunction or myocardial injury [20, 21]. Newer trials suggest a potential role for some form of thrombolysis in these subset of patients [22–24]. Our study does have considerable limitations. The retrospective design of our study introduces some selection bias in our patient sample. It is likely that based on current guidelines most of the patients in our database likely received tPA for a diagnosis of massive PE, as the database and ICD-9 codes do not distinguish between massive and sub-massive PE. We can expect some

attenuation of this bias due to the large sample size of the NIS database. Since the NIS database is limited to in-patient hospital events, delayed bleeding complications would not be included; however, bleeding complications from tPA therapy are usually apparent in the acute phase, as most thrombolytic agents available have a short half-life [25]. Though we reported the in-hospital mortality rate, we could not provide the cause of mortality, which is not provided in the database. The propensity score analysis does not account for unmeasured confounding variables. Our study does not take hemodynamic profiles into account. We did not separate patients with ESRD from those with CKD. Future, prospective randomized studies are needed to assess the safety and efficacy of thrombolysis in the CKD patient with longitudinal data.

Conclusion

To the best of our knowledge, this is the first study to assess the safety of thrombolysis in CKD patients for PE. Our study has considerable limitation. The analysis in the manuscript suggests in a retrospective cohort, the use of thrombolysis is safe and effective in patients with CKD compared to those with normal renal function. Prospective evidence is needed to confirm.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The research was conducted on publicly available database that contains de-identified information. This article does not contain any studies with human participants performed by any of the authors.

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